J Infect Chemother (2011) 17 (Suppl 1):162–164
DOI 10.1007/s10156-010-0163-4

GUIDELINES

Chapter 3-3. Appendix: drug-resistant anaerobes

Introduction

Drug-resistant strains of many bacteria have been reported. Trends in drug resistance of major bacterial strains isolated from clinical materials will be outlined below, citing our own data as well.

Bacteroides fragilis group

Bacteria referred to collectively as the "*Bacteroides fragilis* group (*B. fragilis* group)" are predominant among the anaerobes isolated from clinical materials. Diverse drug-resistant strains have been reported for these bacteria. Most strains of the *B. fragilis* group isolated from clinical cases produce β-lactamase. Originally, the β-lactamase produced by the *B. fragilis* group often extended the spectrum type and manifested diverse resistance to β-lactams such as penicillins and cephems. These strains often show resistance to multiple drugs such as tetracycline (TC), macrolides and fluoroquinolones, in addition to β-lactams. Resistance to clindamycin (CLDM) is seen in 30–40% of the *B. fragilis* group. Bacteria of genus *Bacteroides* other than *B. fragilis*, i.e. non-*B. fragilis* microorganisms such as *B. thetaiotaomicron*, tend to show broader drug resistance than *B. fragilis*. From the viewpoint of drug resistance, the *B. fragilis* group should be divided into *B. fragilis* and non-*B. fragilis*. Except for the occasionally seen highly resistant strains, *B. fragilis* is susceptible to cephamycins, while non-*B. fragilis* is resistant to cephamycins. Drugs which are expected to exert activity against this group of bacteria, and hence should be selected before attempts at empiric therapy, are carbapenems, β-lactams with β-lactamase inhibitor, and some of the new fluoroquinolones planned for clinical introduction in the near future. In cases in which the isolated bacterium has been identified as *B. fragilis*, cephamycins are also expected to be effective. The drug most reliable for such cases is metronidazole, although this drug is not marketed for this purpose in Japan.

It needs to be borne in mind that some strains of the *B. fragilis* group show resistance to these drugs, usually expected to show efficacy against this group, although the frequency of isolation of such resistant strains is low. Particular care is needed of carbapenem-resistant strains. Carbapenem-resistant strains, which exert resistance via metallo-β-lactamase, are highly resistant not only to carbapenems in general but also to β-lactams with a β-lactamase inhibitor, and other all β-lactams (including cephamycin), although such strains have been detected only among the *B. fragilis*. It is not uncommon for these strains to also show resistance to CLDM and TC. In any event, it is essential to seek drugs to which these strains are susceptible among drugs of this and other families. Moderate resistance to carbapenems is seen among some strains of both *B. fragilis* and non-*B. fragilis*. These strains are likely to show resistance to β-lactams in general, but some *B. fragilis* strains are susceptible to cephamycin.

Genus *Prevotella*

β-Lactamase-producing bacteria of genus *Prevotella* tend to show resistance to β-lactams, similar to the resistance exhibited by *B. fragilis*. In fact, the percentage of β-lactamase-producing strains is close to 90% for non-pigmented *Prevotella*, such as *P. bivia*. These strains show resistance to many β-lactams, excluding cephamycin, β-lactams with β-lactamase inhibitors, and carbapenems.

The MIC of the drugs, to which these strains show resistance, is high for all of these strains. Among the black-pigmented bacteria of genus *Prevotella* such as *P. intermedia*, about 60% now produce β-lactamase, although very few of these bacteria produced β-lactamase in the past. Although the resistance of bacteria of genus *Prevotella* is not as high as that of *B. fragilis*, the MIC of β-lactams (penicillins, cephams, etc.) against these β-lactamase-producing strains of *Prevotella* is markedly higher than that against non-β-lactamase-producing strains. Moderate or higher resistance is exhibited by these strains. Resistance to carbapenems has been reported for *P. nigrescens*, *P. intermedia*, *P. melaninogenica* and *P. oralis* isolated from dental patients [1]. Regarding resistance of *Prevotella* to other drugs, it is known that 15–30% of *Prevotella* strains show resistance to fluoroquinolones (developed many years ago and since used frequently) and about 40% show resistance to TC. Resistance to CLDM is seen in about 10% of all *Prevotella* strains.

Genus *Fusobacterium*

Bacteria of genus *Fusobacetrium* often isolated from clinical materials are *F. nucleatum*, *F. varium* and *F. mortiferum*. All three of these bacteria are resistant to macrolides. Like *B. fragilis*, *F. varium* and *F. mortiferum* show resistance to various antibacterial agents. At present, however, these bacteria are mostly susceptible to CLDM. *F. nucleatum* does not show extensive resistance, unlike *F. varium* and *F. mortiferum*, but not a few strains of *F. nucleatum* show high resistance to certain penicillins.

Bilophila wadsworthia, *Sutterella wadsworthensis* and genus *Desulfovibrio*

All of these bacteria grow slowly and form small colonies. They tend to be overlooked if samples are cultured with non-selective medium alone. These bacteria show resistance to certain drugs, including those used for the treatment of anaerobic infections.

B. wadsworthia began to attract clinical attention relatively recently. Its isolation from cases with intraperitoneal infections and various other infections has been reported. This bacterium produces β-lactamase and shows resistance to β-lactams (particularly penicillins). The resistance of this bacterium to drugs is affected by the bacterial density in individual cases. This bacterium tends to also be resistant to macrolides. *S. wadsworthensis*, also isolated from intraperitoneal infection cases, does not grow in carbon dioxide culture but grows well in microaerophilic environments. This bacterium is resistant to metronidazole [2]. Bacteria of genus *Desulfovibrio* are reportedly resistant to some penicillins and cephems [3].

Genus *Clostridium*

C. perfringens shows resistance only to a small number of drugs, but some strains of this bacterium are resistant to TC and CLDM. Bacteria of genus *Clostridium* other than *C. perfringens* occasionally show resistance to macrolides, TCs, CLDM and cephems. It is well known that *C. difficile*, responsible for antibacterial drug-associated diarrhea, is highly resistant to multiple drugs. Other bacteria of genus *Clostridium* which are often isolated from clinical materials and require caution because of drug resistance are *C. ramosum*, *C. innocum* and the *C. clostridioforme* group (*C. clostridioforme*, *C. bolteae*, *C. hathewayi*, etc.).

Anaerobic gram-positive cocci

Until recently, *Peptostreptococcus anaerobius* (one of the anaerobic gram-positive cocci isolated at a high frequency) and three other bacteria (*Finegoldia magna*, *Parvimonas micra* and *Peptoniphilus asaccharolyticus*) were regarded as belonging to the same genus (*Peptostreptococcus*). For this reason, the susceptibilities of these four bacteria tend to be discussed collectively in the context of the susceptibility of genus *Peptostreptococcus*. In practice, however, drug susceptibilities differ among these four bacteria. *P. anaerobius*, *P. asaccharolyticus* and *F. magna* are resistant to some β-lactams. *P. anaerobius* tends to show resistance more frequently than the others. Resistance to macrolides and certain fluoroquinolones is more common with *P. asaccharolyticus* and *F. magna* than with the others. Furthermore, *P. micra* shows resistance to various drugs although not at a high frequency.

Atopobium vaginae

Atopobium vaginae is another bacterium, in addition to those listed above, for which knowledge regarding drug resistance would be desirable. This is a recently discovered anaerobic gram-positive rod (described as a "coccus" in some reports), suggested as one of the pathogens for bacterial vaginosis. This bacterium does not require strictly anaerobic environments for its growth and is hence resistant to metronidazole [4].

References

1. Nakatsuji T. Exploration of β-lactamase gene in Prevotella using PCR—based on analysis of carpenemase gene derived from *Prevotella nigrescens* TO167. Jpn J Chemother. 2002;50:16–24. (Japanese).
2. Wexler HM, Reeves D, Summanen PH, Molitoris E, McTeague M, Duncan J, et al. Sutterella wadsworthensis gen. nov., sp. Nov., bile-resistant microaerophilic *Campylobacter gracilis*-like clinical isolates. Int J Syst Bacteriol. 1996;46:252–8.
3. Lozniewski A, Labia R, Haristoy X, Mory F. Antimicrobial susceptibilities of clinical Desulfovibrio isolates. Antimicrob Agents Chemother. 2001;45:2933–5.
4. Ferris MJ, Masztal A, Aldridge KE, Fortenberry JD, Fidel PL Jr., Martin DH. Association of *Atopobium vaginae*, a recently described metronidazole resistant anaerobe, with bacterial vaginosis. BMC Infect Dis 2004;4:5. Available from: http://www.biomedcentral.com/1471-2334/4/5.